# Ekogenetik ve Çevresel Faktörlere Yanıtın Bireysel Farklılıklarında Genetiğin Rolü

Kistik fibroz

Travma

Kanser

Sağırlık

Renk körlüğü

Enfeksiyon

Diabetes mellitus

Fenilketonüri

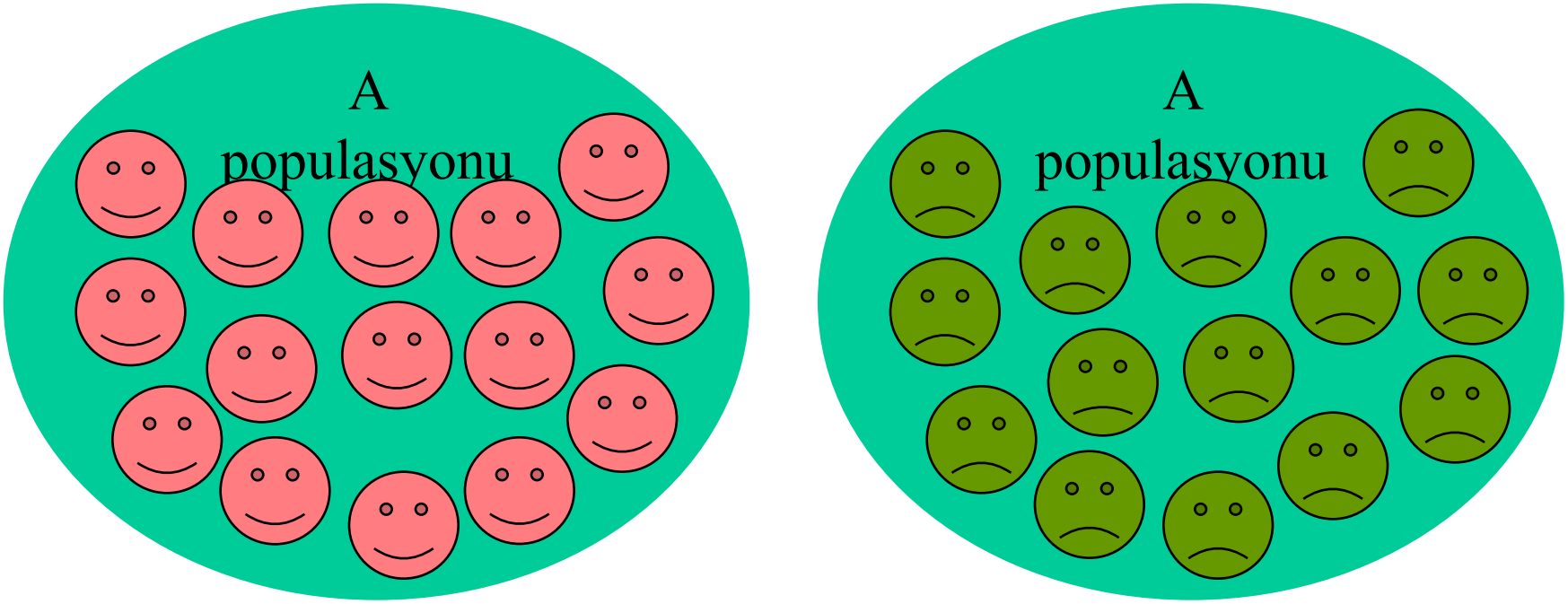
Entoksikasyon

**KALITIM (genetik)**

**ÇEVRESEL**

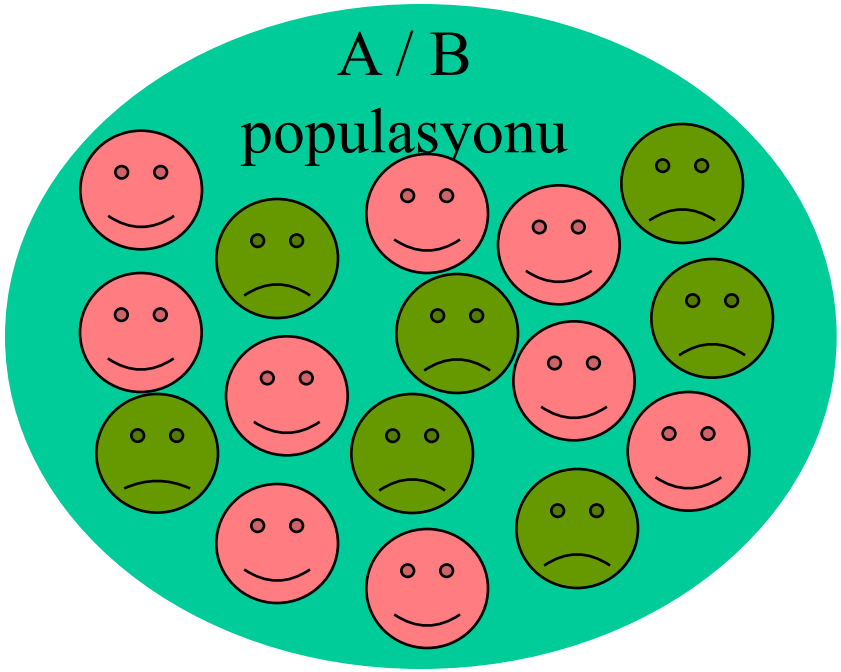
# Populasyon Farklılıkları

- Aynı genetik altyapıya sahip farklı çevre koşullarında yaşayan topluluklar



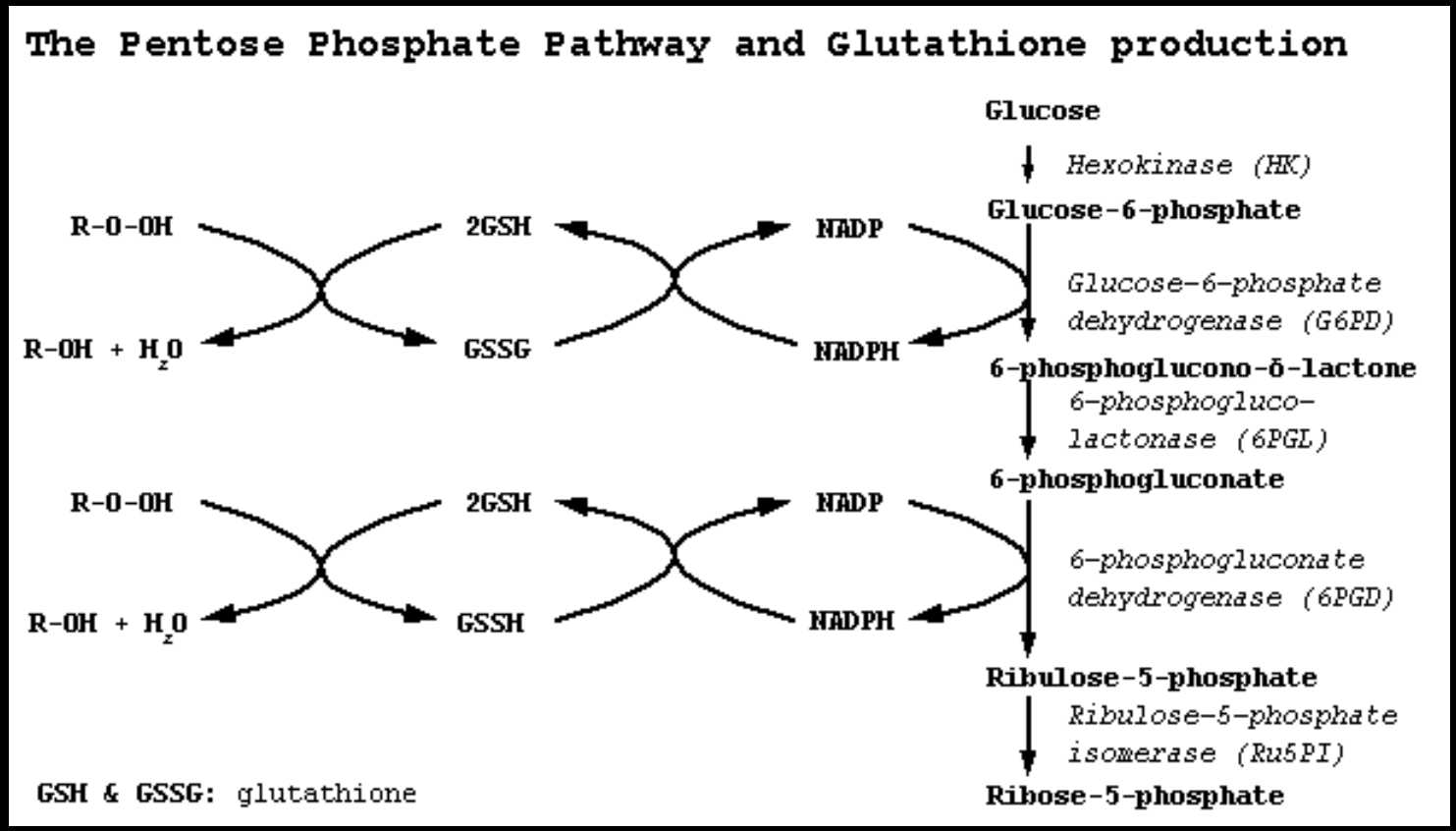
# Genetik Farklılıklar

- Farklı genetik altyapıya sahip aynı çevre koşullarında yaşayan bireyler

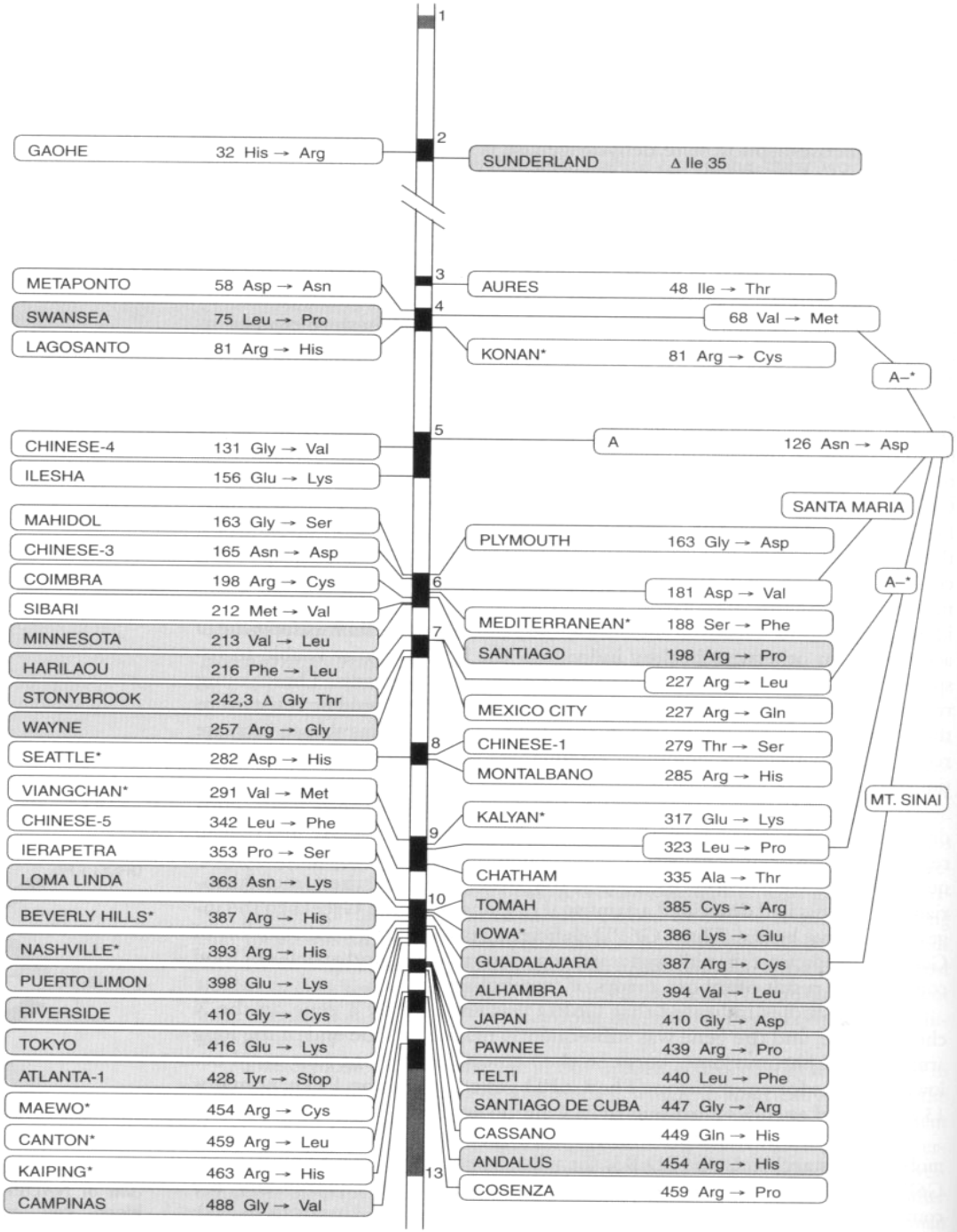


# Ekogenetik açıdan insanlardaki önemli polimorfizmler

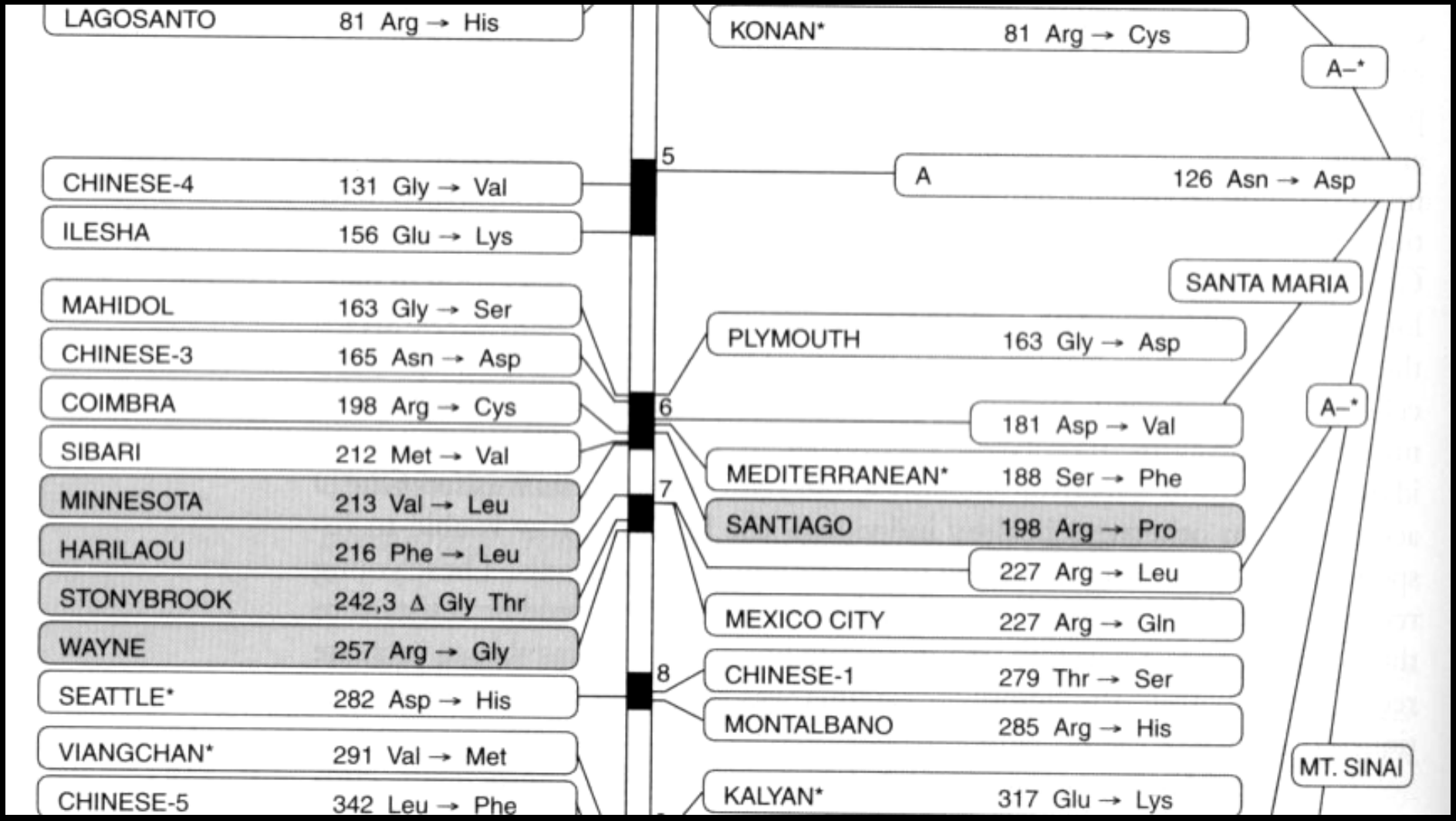
- Hemoglobin varyantları (HbS – homozigotlarda orak hücreli anemi, heterozigotlarda malarya enfestasyonuna direnç)
- Glukoz-6-dehidrogenaz (G6PD) eksikliği (bazı ilaçlara ve fasülye gibi gıda tüketimine bağlı hemolitik kriz)
- Laktaz aktivitesi farklılıkları (süt tüketiminde laktoz intoleransı)

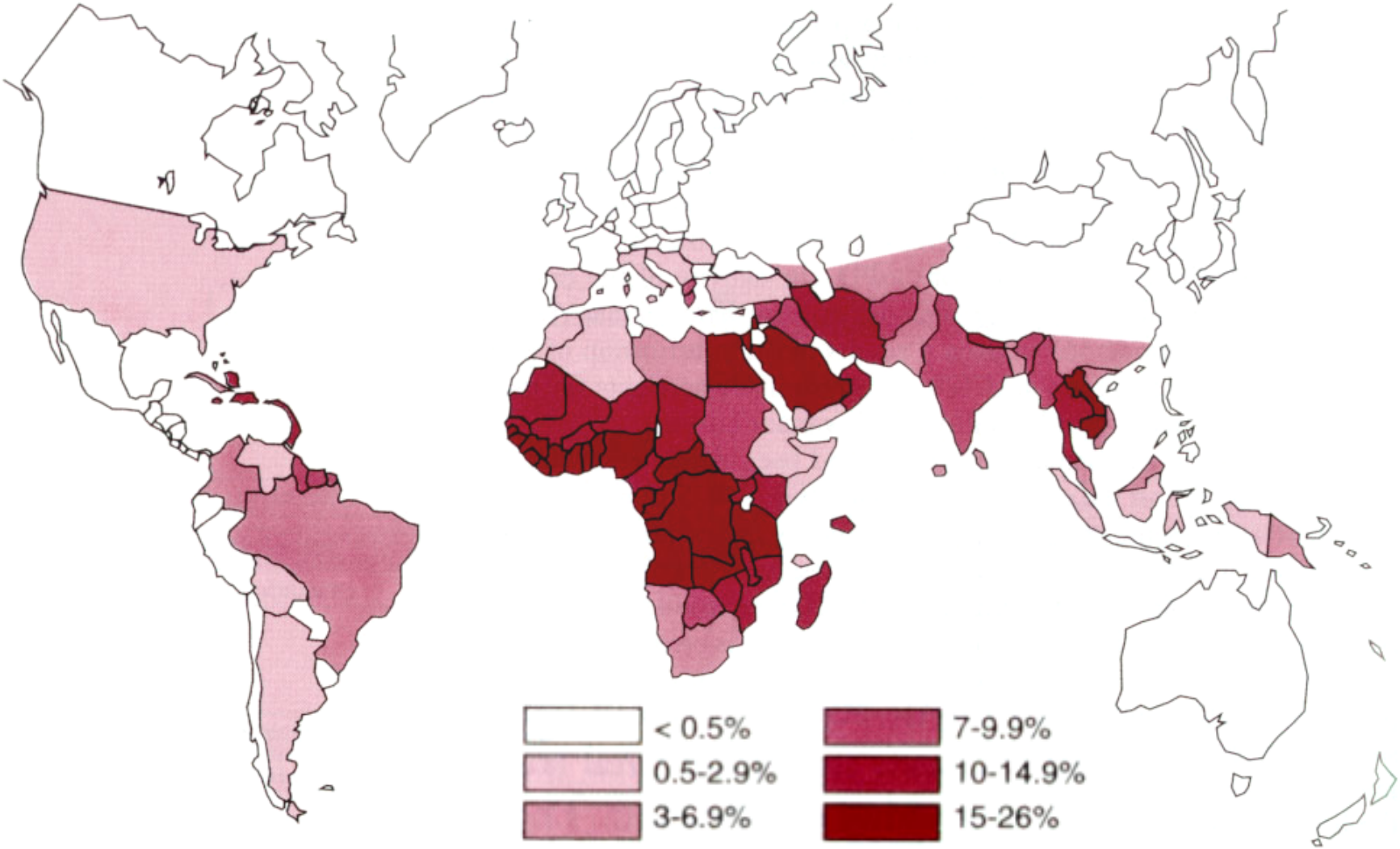



Eritrositlerin oksidatif zarardan korunmasında G6PD'nin rolü.

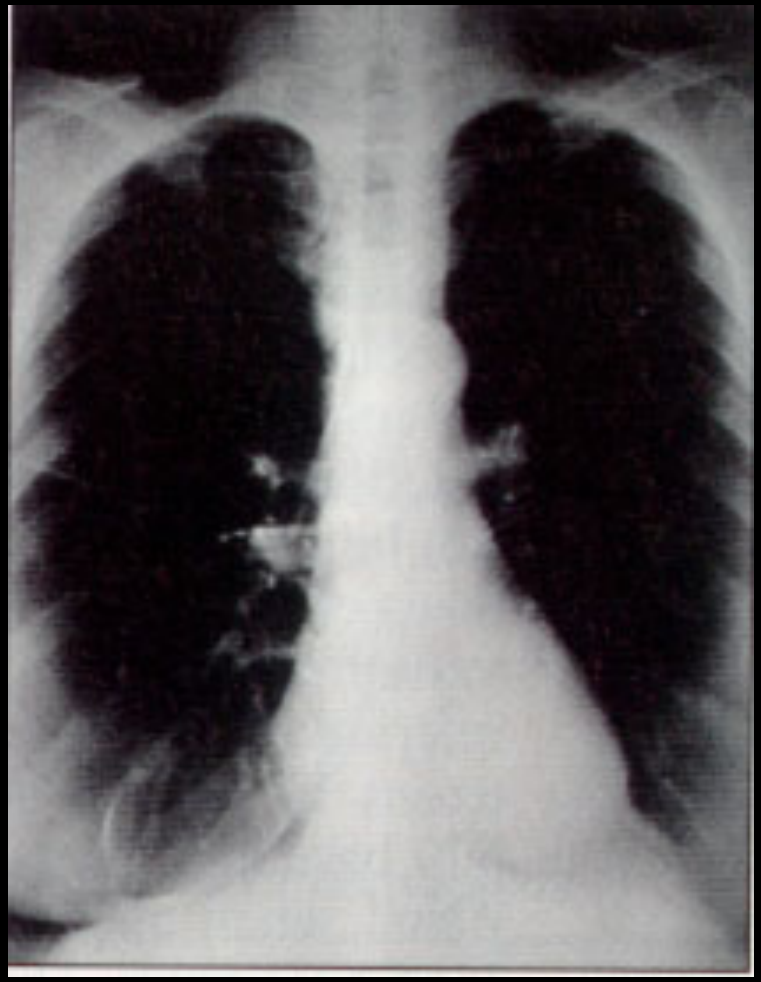



# G6PD mutasyonları


LAGOSANTO 81 Arg → His
KONAN* 81 Arg → Cys
A–*
5
CHINESE-4 131 Gly → Val
ILESHA 156 Glu → Lys
A 126 Asn → Asp
SANTA MARIA
MAHIDOL 163 Gly → Ser
CHINESE-3 165 Asn → Asp
COIMBRA 198 Arg → Cys
SIBARI 212 Met → Val
MINNESOTA 213 Val → Leu
HARILAOU 216 Phe → Leu
STONYBROOK 242,3 Δ Gly Thr
WAYNE 257 Arg → Gly
SEATTLE* 282 Asp → His
VIANGCHAN* 291 Val → Met
CHINESE-5 342 Leu → Phe
PLYMOUTH 163 Gly → Asp
6
181 Asp → Val
A–*
MEDITERRANEAN* 188 Ser → Phe
7
SANTIAGO 198 Arg → Pro
227 Arg → Leu
MEXICO CITY 227 Arg → Gln
8
CHINESE-1 279 Thr → Ser
MONTALBANO 285 Arg → His
MT. SINAI
KALYAN* 317 Glu → Lys




G6PD eksikliğinin dünyada dağılımı



Alfa-1antitripsin enzim eksikliği

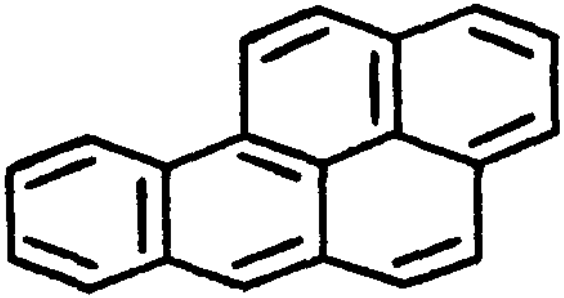
*Lökosit elastazın alveoler elastini baskılayamaması ile obstrüktif pulmoner anfizem ilişkisi*

# Klinik Açıdan Önemli alfa-1 antitripsin genotipleri

| Pi Genotipleri | MM | MZ | SS | SZ | Z Glu342Lys |
|---|---|---|---|---|---|
| Frekans | 0.90 | 0.038 | 0.001 | 0.0012 (1/800) | 0.0004 (1/2500) |
| Aktivite (%kontrol) | 100 | 60 | 50-60 | 30-35 | 10-15 |

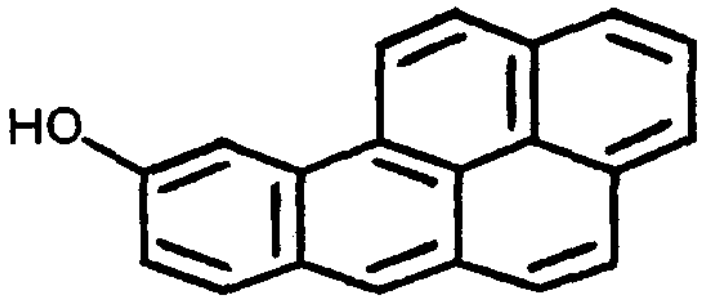
# Ekogenetik açıdan insanlardaki önemli polimorfizmler

- Asetaldehitdehidrogenaz (ALDH) aktivitesi farklılıkları (etanol tüketiminde intolerans, bazı Uzak Doğu ve Güney Amerika topluluklarında gözlenir)
- Sitokrom P450-monooksijenaz –xenobiyotiklerin (karsinojen ve mutajenler) oksidasyonu farklı enzim izoformları nedeniyle yetersiz olabilir
- Arilhidrokarbon hidroksilaz (AHH) ile aromatik hidrokarbonların epoksi bileşiklere dönüşümü ile karsinojenik etki oluşumu



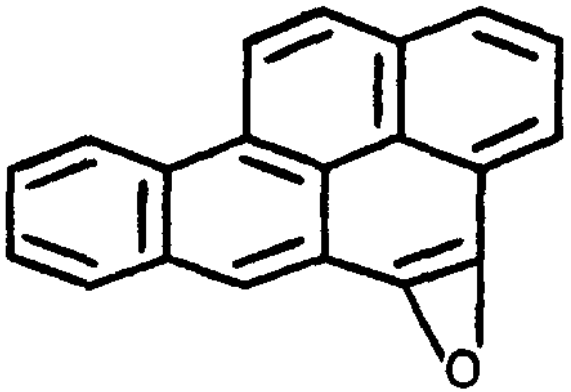
Benzo ($\alpha$) pyrene

AHH activity

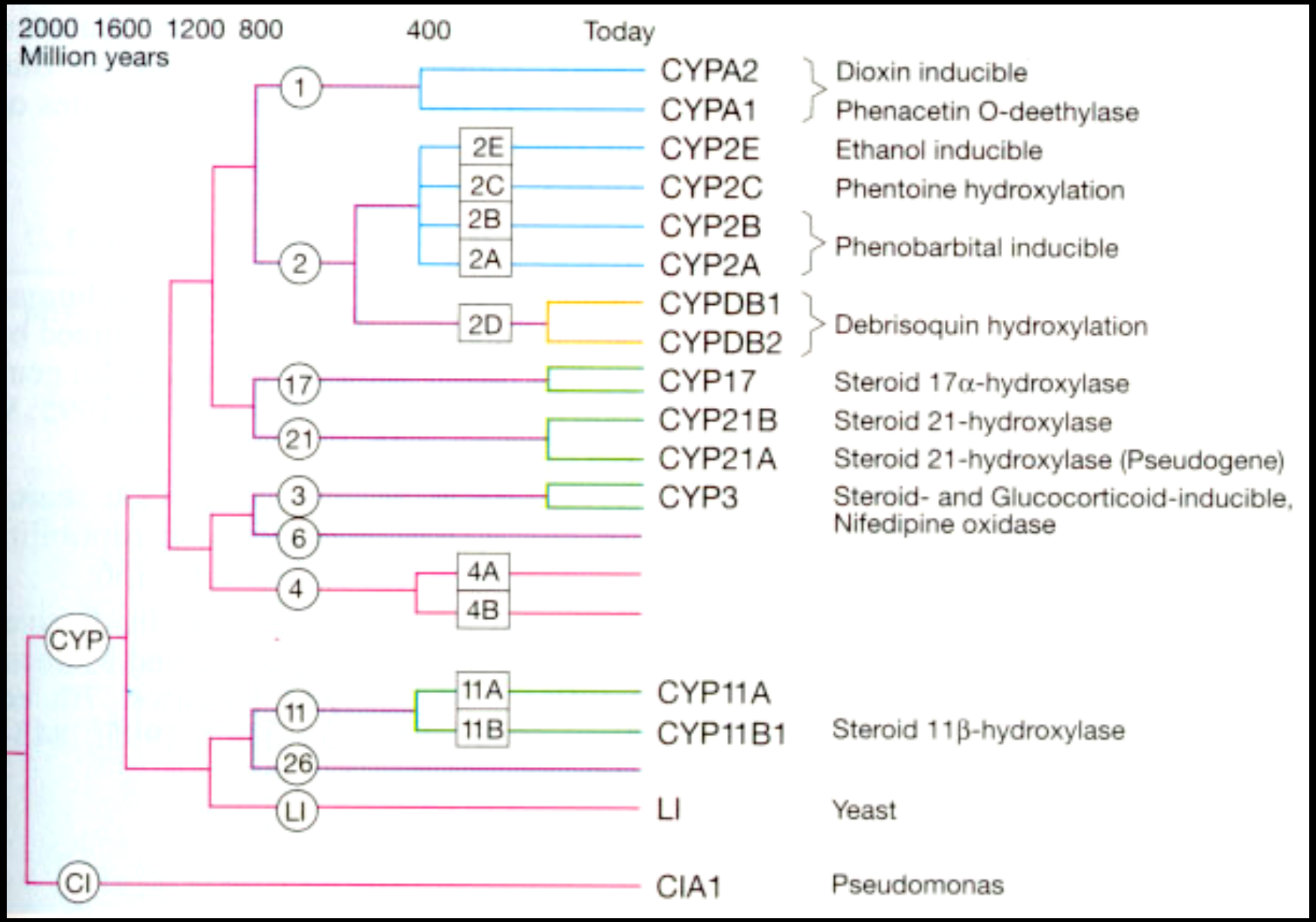



A phenol

AHH activity



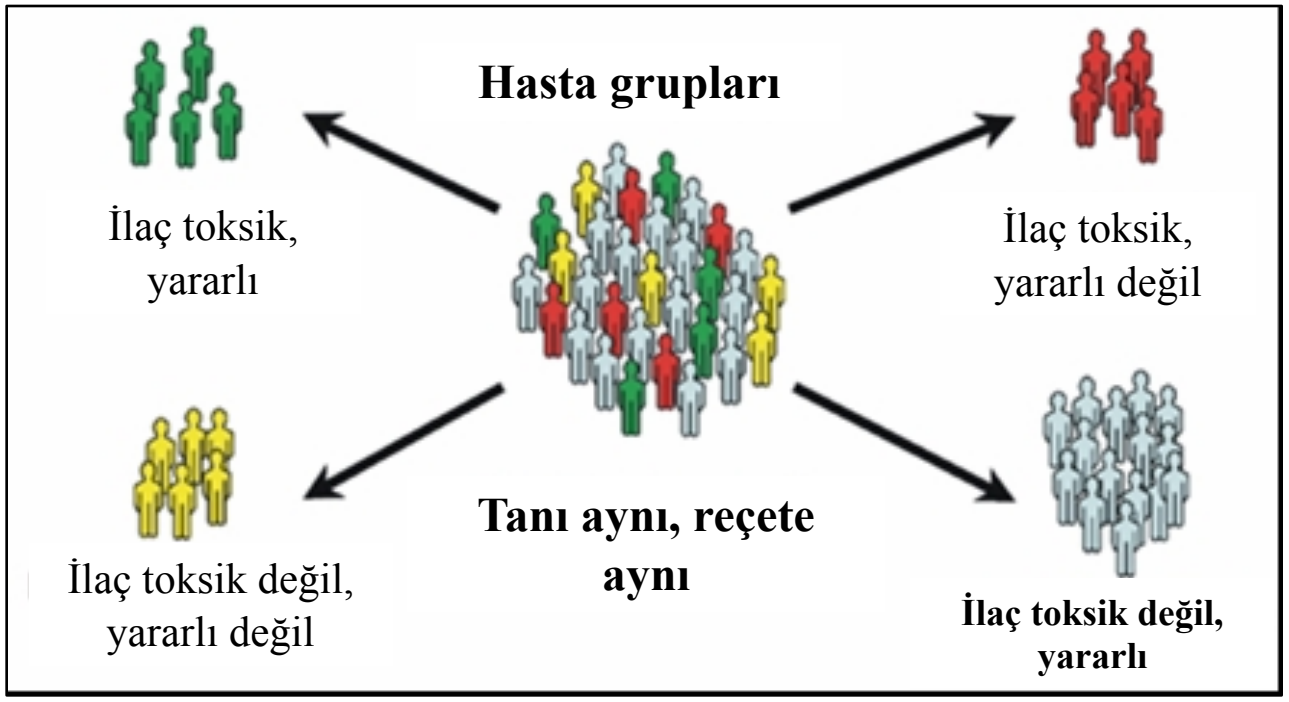

An epoxide




**CYP süpergen ailesi**

# Kişisel Tıp

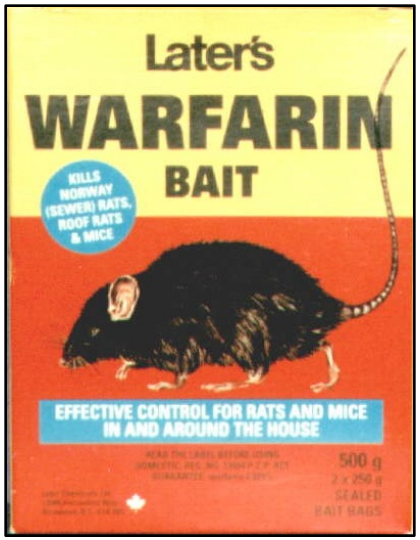
## *Tedaviye Yanıtta Farklılıklar*



# Örnek: Warfarin

Antikoagulan,
tromboz oluşumunu
engellemede etkin

# Warfarin



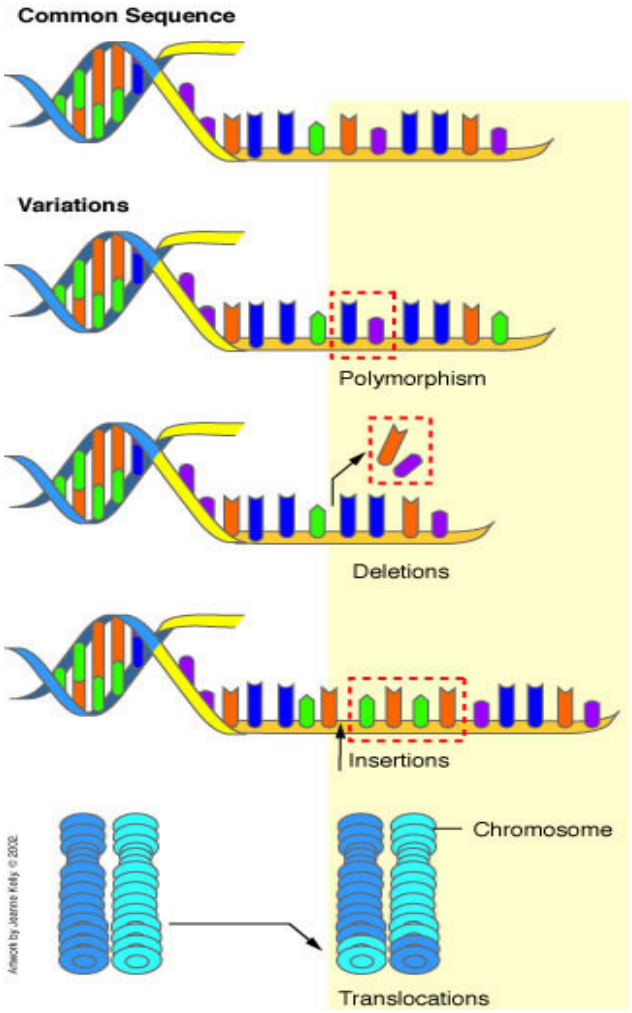

Warfarin fare zehiri olarak
Kullanılan bir kimyasal

Optimal doz toplumdan topluma değişiyor

Genetik varyantlar (VKORC1, CYP2C9)
optimal kişisel dozu etkiliyor

# Varyasyon Çeşitleri

- SNP
- Kopya Sayısı Varyasyonları (CNV)
- Delesyon
- İnsersiyon
- Translokasyon



# SNP

- Single (Tek) Nucleotide Polymorphism
- İnsanın evrimsel süreçinin bir parçası
- İnsanda DNA polymorfizmlerinin %90'ı
- Sıklığı tahminen 1/600 – 1000 bç
- Çoğunluğu intronlarda (2/3)
  - Regulatör bölgeler (kanser, nöropsikiatri)
- Ekzonlarda letal olabilir (1/3)
  - Fatal aminoasit değişiklikleri

Hastalığa dirençli

Hastalığa duyarlı

Binlerce SNP için bireylerde genotip çalışması

ATGATTATAG

*X geni*

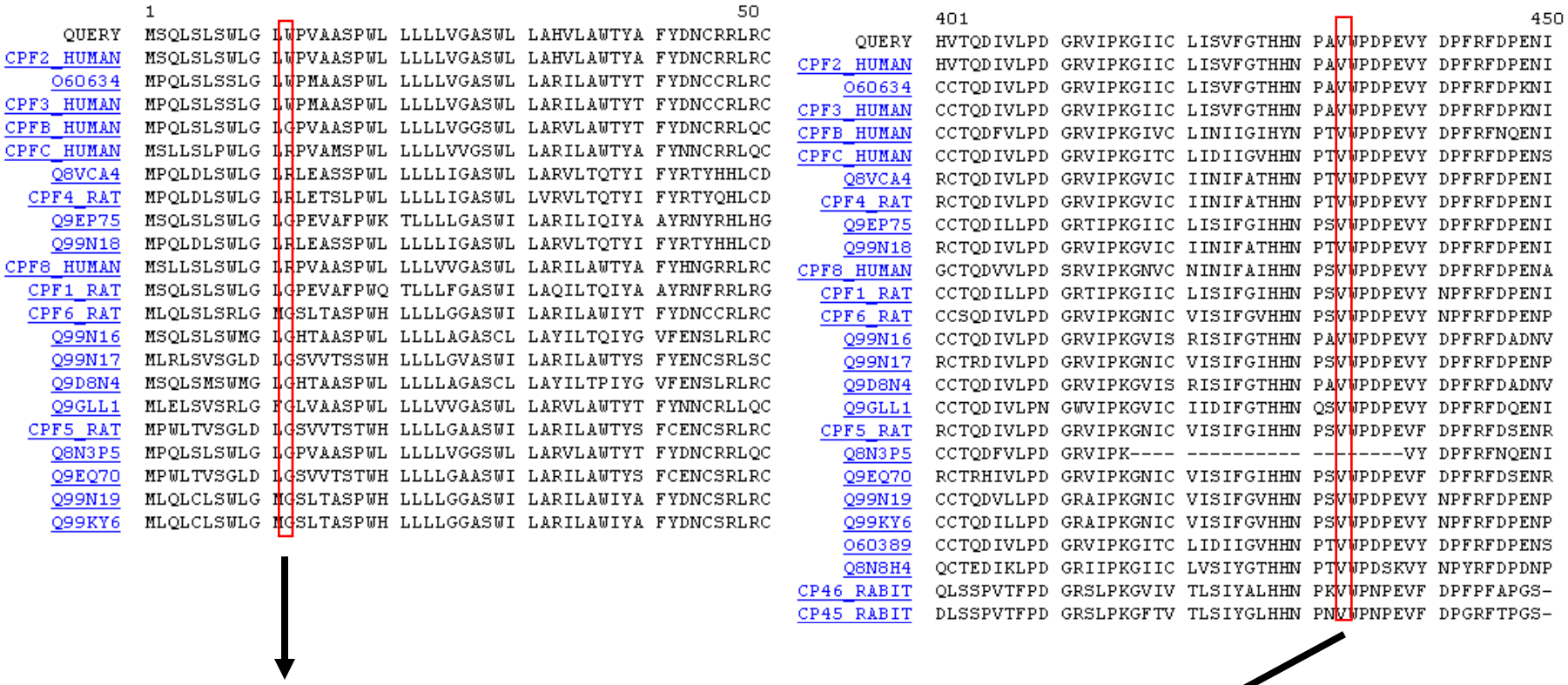
ATGTTTATAG

Dirençlilerde X *geni* 4. Pozisyonunda hep “A”
duyarlılarda ‘T’ (SNPler :A/T)

# SNP Uygulamaları

- Gen keşfi, haritalama
- Asosiyasyon temelli aday gen çalışmaları
- Tanı / risk profili
- İlaç tanıt tahmini
- Gen işlev çalışmaları

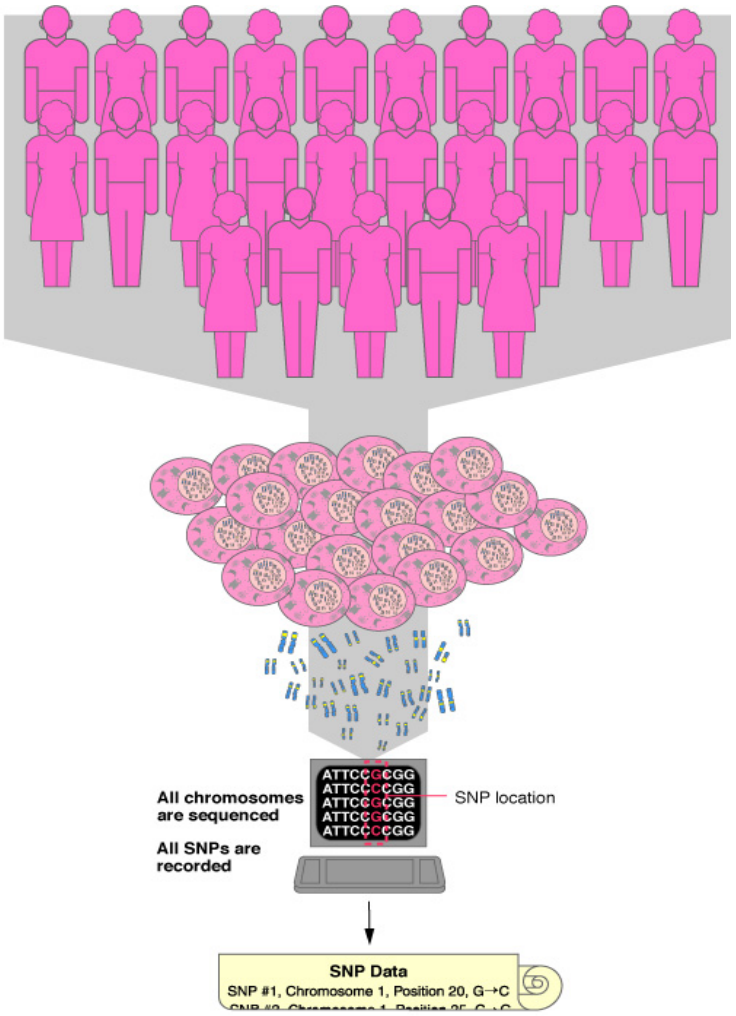
# CYP4F2:sitokrom 450, altgrup IVF polipeptid 2

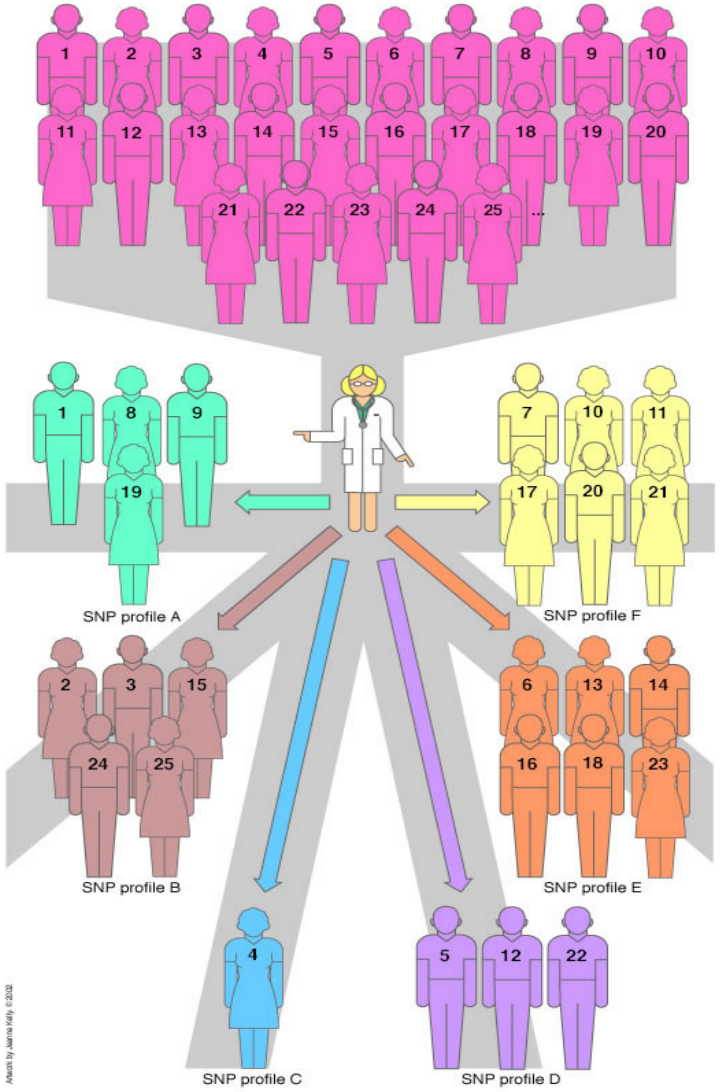



Trp (W) → Gly (G) Val (V) → Gly (G)

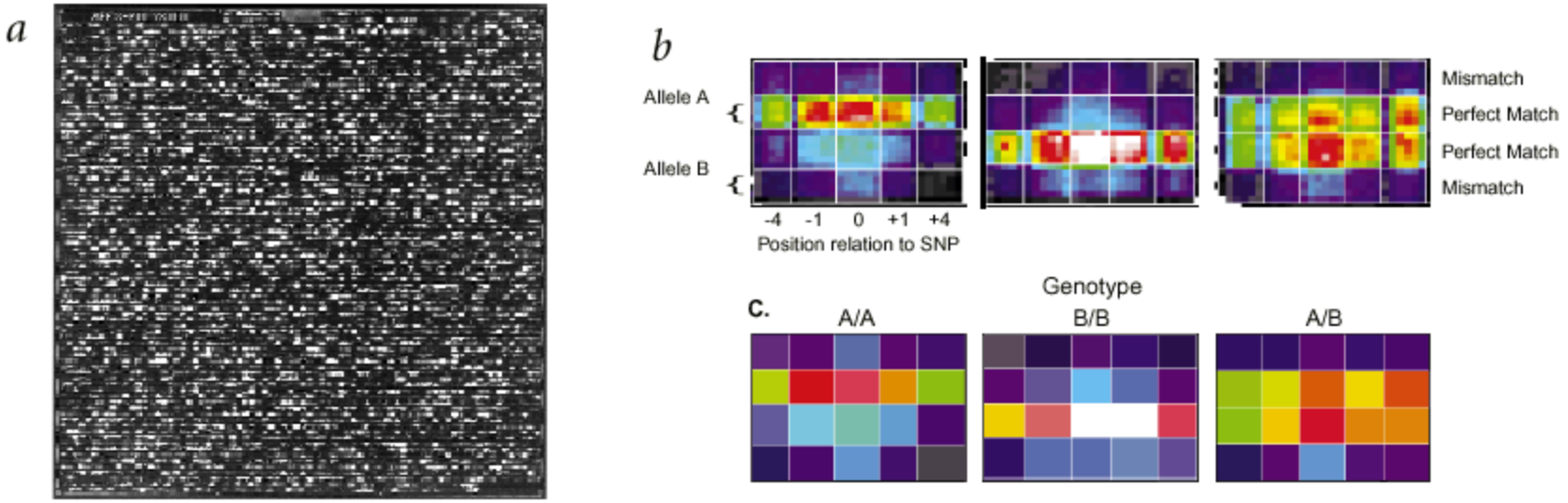
\+ Warfarin toleransı -

# SNP'ler ile saptanan populasyon farklılıkları



# SNP Genotipleme




Mikroarray temelli yüksek verimli SNP çalışmaları

dbSNP Home Page - Microsoft Internet Explorer

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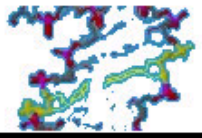
Address http://www.ncbi.nlm.nih.gov/SNP/ Go Links

NCBI

# Single Nucleotide Polymorphism



PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM Books SNP

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- Handle Request

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- FAQ
- Overview
- How to Submit
- RefSNP Summary Info
- Database Schema
  - pdf
  - Changes NEW
- Data Formats
- Heterozygosity
- Computation

SEARCH

## dbSNP Search Options

Entrez SNP | ID Numbers | Submission Info | Batch | Locus Info | Free Form | Easy Form | Between Markers

ANNOUNCEMENT

- NEW! dbSNP genotype data are now available on the web and on our FTP site (more info).
- ALERT! xml brief and submission format reports are dropped from ftp dump starting build 116. Please contact snp-admin with concerns.

## Search by IDs

Note: rs# and ss# must be prefixed with "rs" or "ss", respectively (i.e. rs25, ss25)

Reference cluster ID(rs#)

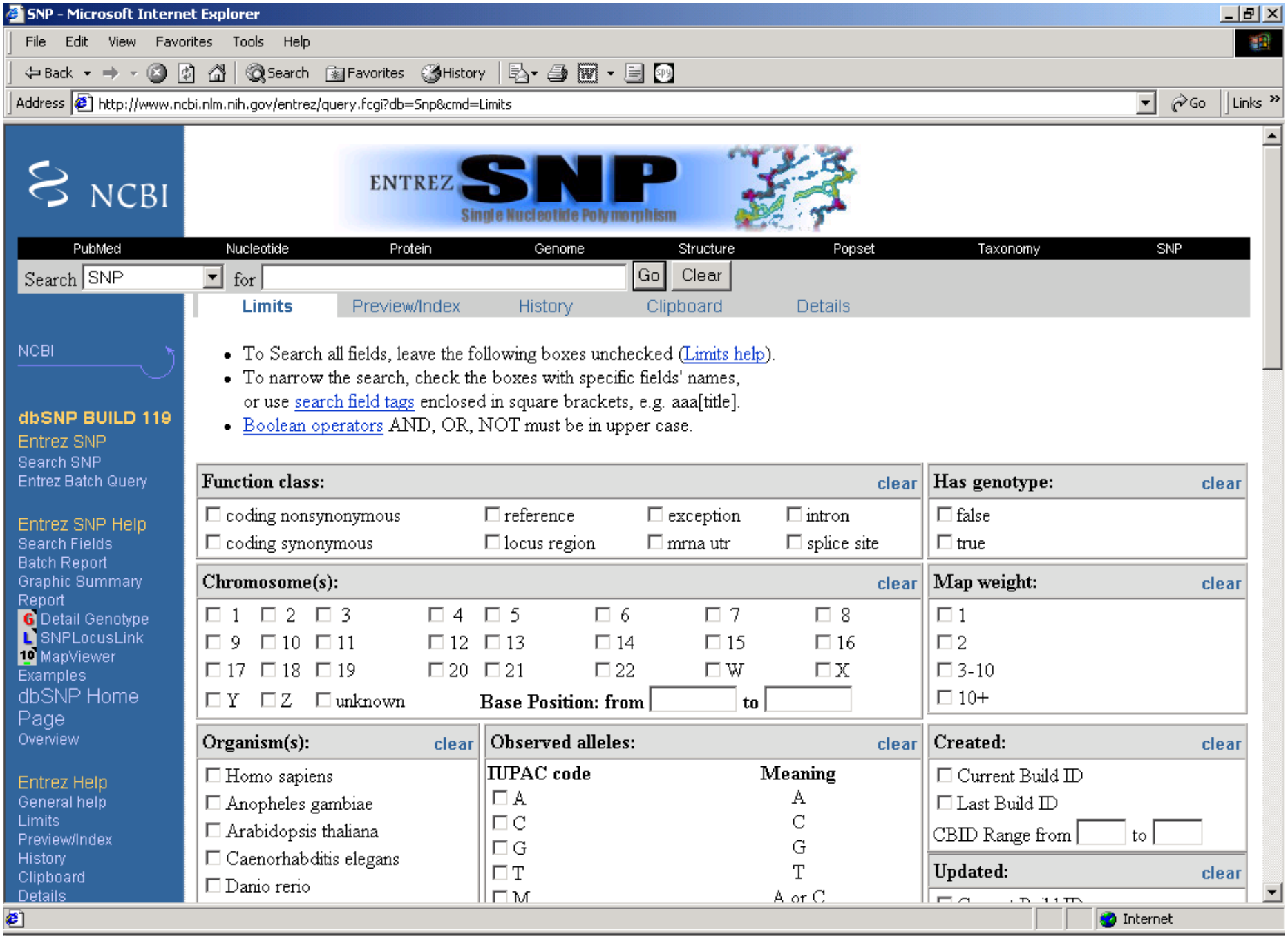
Search Reset

Advanced ID Search

## Submission Information

- By Submitter
- New Batches

Done Internet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Single Nucleotide Polymorphism
PubMed Nucleotide Protein Genome Structure Popset Taxonomy SNP
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NCBI
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Search SNP
Entrez Batch Query
Entrez SNP Help
Search Fields
Batch Report
Graphic Summary Report
Detail Genotype
SNPLocusLink
MapViewer
Examples
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Limits
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Clipboard
Details
To Search all fields, leave the following boxes unchecked (Limits help).
To narrow the search, check the boxes with specific fields' names, or use search field tags enclosed in square brackets, e.g. aaa[title].
Boolean operators AND, OR, NOT must be in upper case.
Function class: clear
coding nonsynonymous
coding synonymous
reference
locus region
exception
mrna utr
intron
splice site
Has genotype: clear
false
true
Chromosome(s): clear
1 2 3 4 5 6 7 8
9 10 11 12 13 14 15 16
17 18 19 20 21 22 W X
Y Z unknown
Base Position: from to
Map weight: clear
1
2
3-10
10+
Organism(s): clear
Homo sapiens
Anopheles gambiae
Arabidopsis thaliana
Caenorhabditis elegans
Danio rerio
Observed alleles: clear
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Current Build ID
Last Build ID
CBID Range from to
Updated: clear
Internet

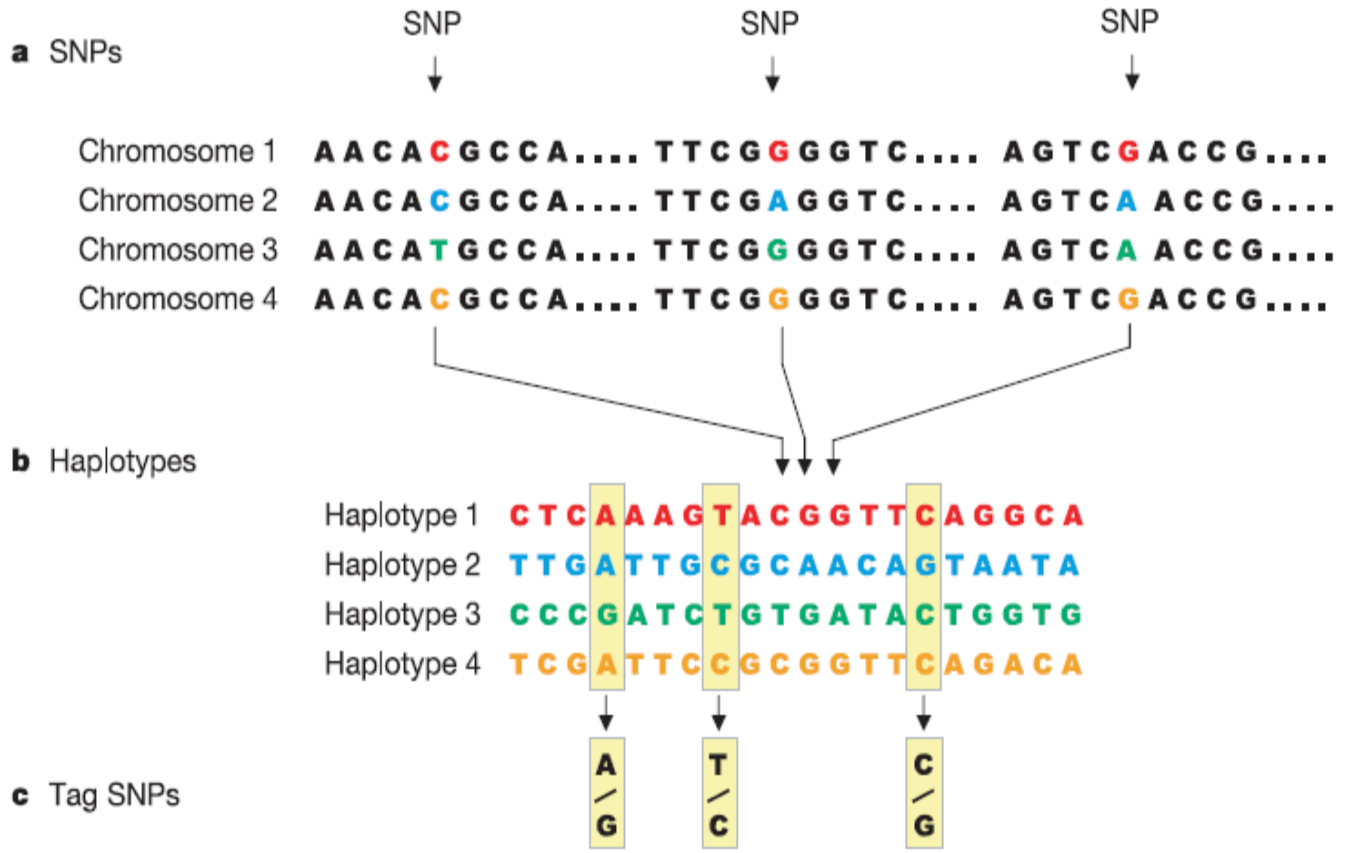



**Figure 1** SNPs, haplotypes and tag SNPs. **a**, SNPs. Shown is a short stretch of DNA from four versions of the same chromosome region in different people. Most of the DNA sequence is identical in these chromosomes, but three bases are shown where variation occurs. Each SNP has two possible alleles; the first SNP in panel **a** has the alleles C and T. **b**, Haplotypes. A haplotype is made up of a particular combination of alleles at nearby SNPs. Shown here are the observed genotypes for 20 SNPs that extend across 6,000 bases of DNA. Only the variable bases are shown, including the three SNPs that are shown in panel **a**. For this region, most of the chromosomes in a population survey turn out to have haplotypes 1–4. **c**, Tag SNPs. Genotyping just the three tag SNPs out of the 20 SNPs is sufficient to identify these four haplotypes uniquely. For instance, if a particular chromosome has the pattern A–T–C at these three tag SNPs, this pattern matches the pattern determined for haplotype 1. Note that many chromosomes carry the common haplotypes in the population.

International HapMap Project, Nature 2003

# Haplotipler – SNP Barkodu


**ATGGTAAGCCTGAGCTGACTTAGCGT-AT**

**ATGGTAAACCTGAGTTGACTTAGCGTCAT**


# International HapMap Project



The International HapMap Project is a partnership of scientists and funding agencies from Canada, China, Japan, Nigeria, the United Kingdom and the United States to develop a public resource that will help researchers find genes associated with human disease and response to pharmaceuticals. See "**About the International HapMap Project**" for more information.

## Project Information

About the HapMap Project
HapMap Project Data
HapMap mailing list
HapMap Project Participants

## Useful Links

HapMap Project Press Release
NHGRI HapMap Page
NCBI Variation Database (dbSNP)
Japanese SNP database (JSNP)

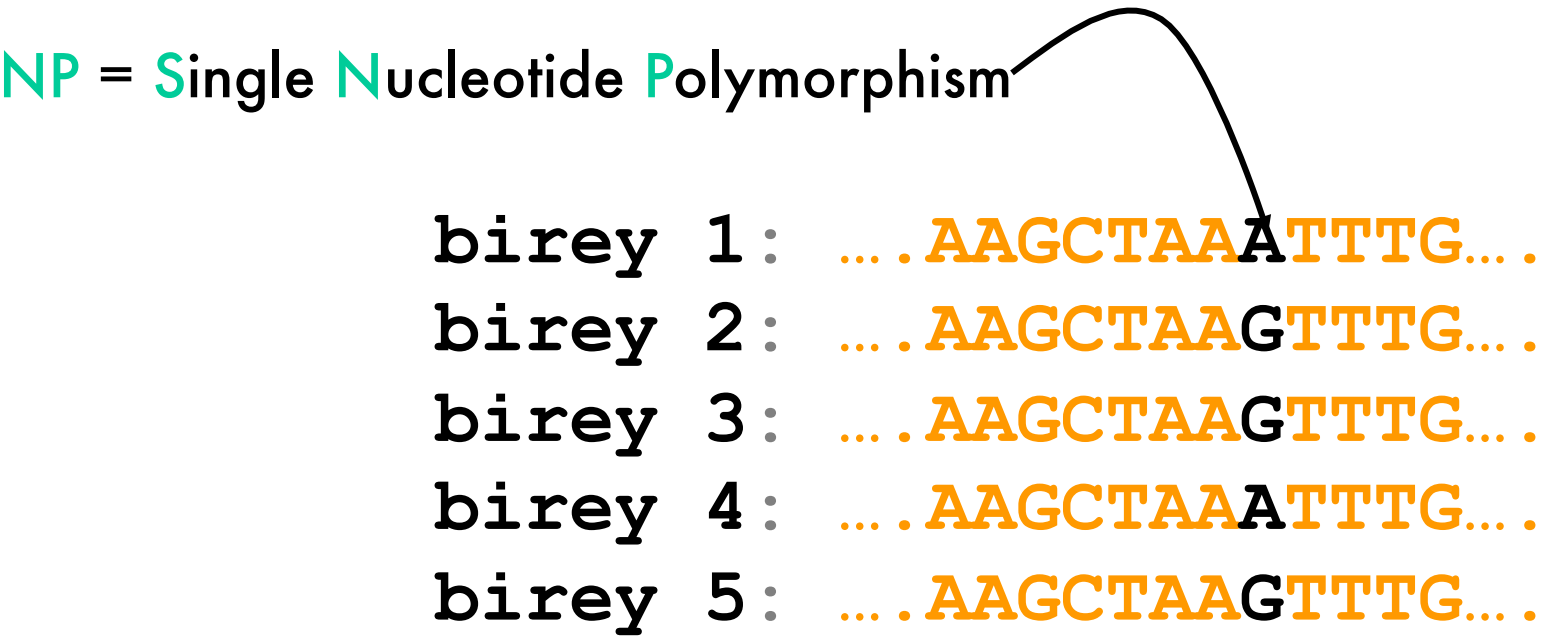
## News

- *2004-03-05* : ***Public data release #5!***
  Genotypes, frequencies and assays for 369,784 SNPs (33,280,560 genotypes) released for **bulk download** and **graphical browsing**.
- *April 18-20, 2004*: **International HapMap Community Analysis Meeting**

  This meeting will discuss data analysis and methodological issues relevant to the International Haplotype Map Project. This will include approaches to describing linkage disequilibrium, properties of linkage disequilibrium, inference of haplotypes and haplotype frequencies, and methods for utilizing the haplotype map in association and other disease studies. The meeting will provide an important opportunity for a diverse community of investigators (both those involved directly in the project, and those in the broader community) to come together to define and debate a range of issues in the creation of the Haplotype Map resource.

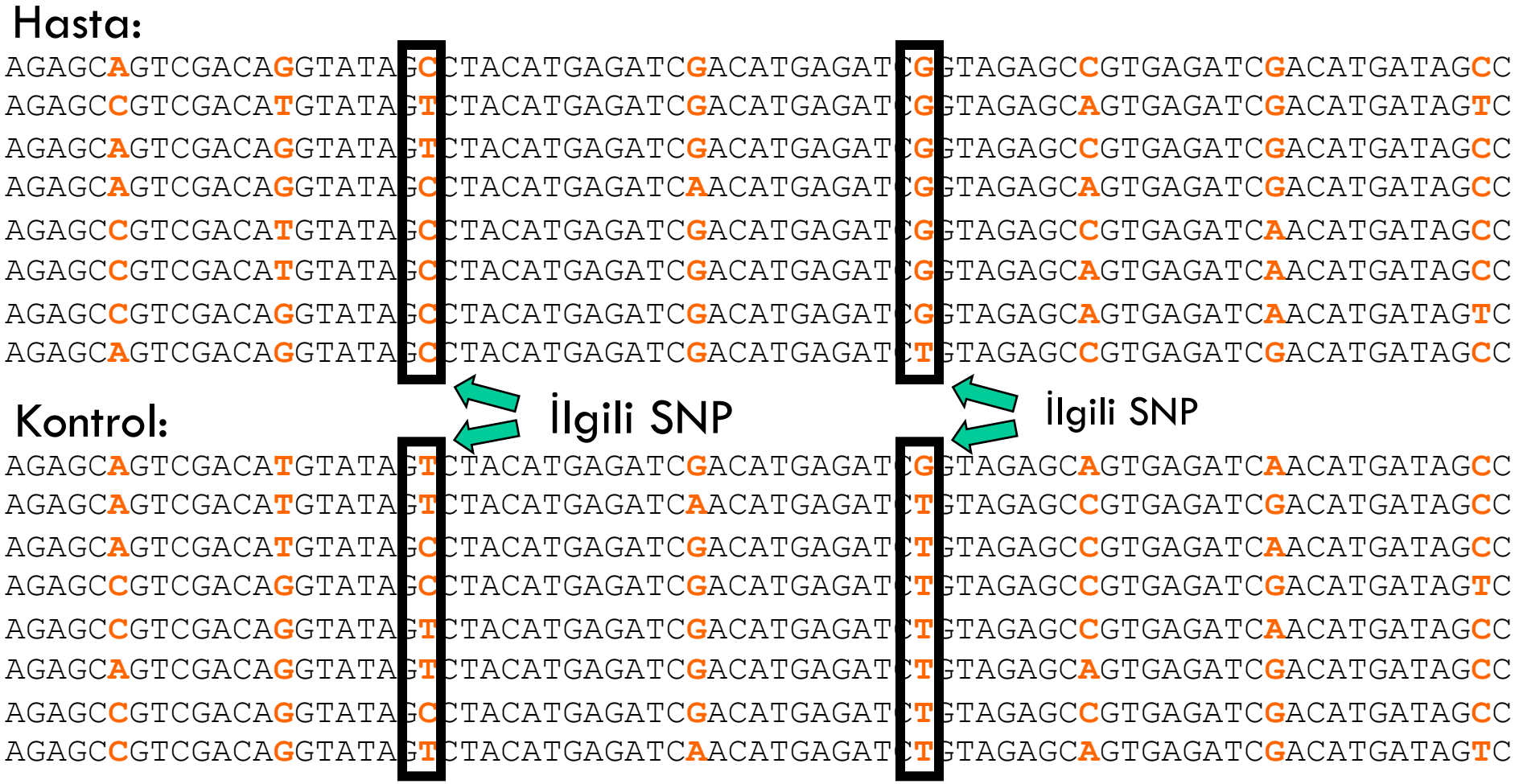
  The meeting is scheduled to begin with presentations and a reception from 6pm on April 18, and will conclude no later than 3pm on April 20. It is being hosted by the McKusick-Nathans Institute of Genetic Medicine/Johns Hopkins University and the National Human Genome Research Institute. For further details, to register, and/or to submit an abstract visit **International HapMap Community Analysis Meeting** website.

SNP = Single Nucleotide Polymorphism




Çoğu SNP için iki alel bulunur.

# Asosiyasyon Çalışmaları



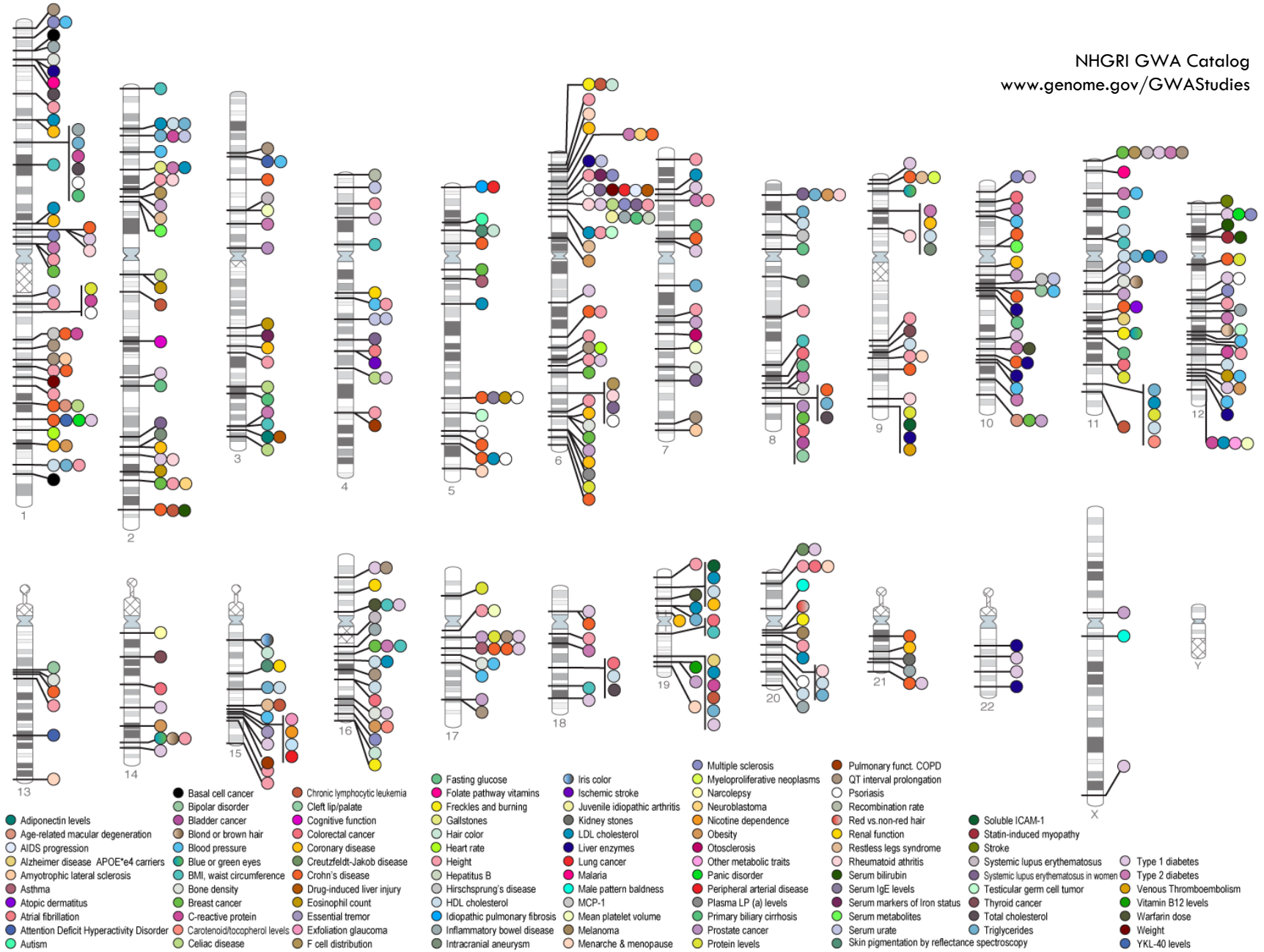
# Genotipleme


**DNA**

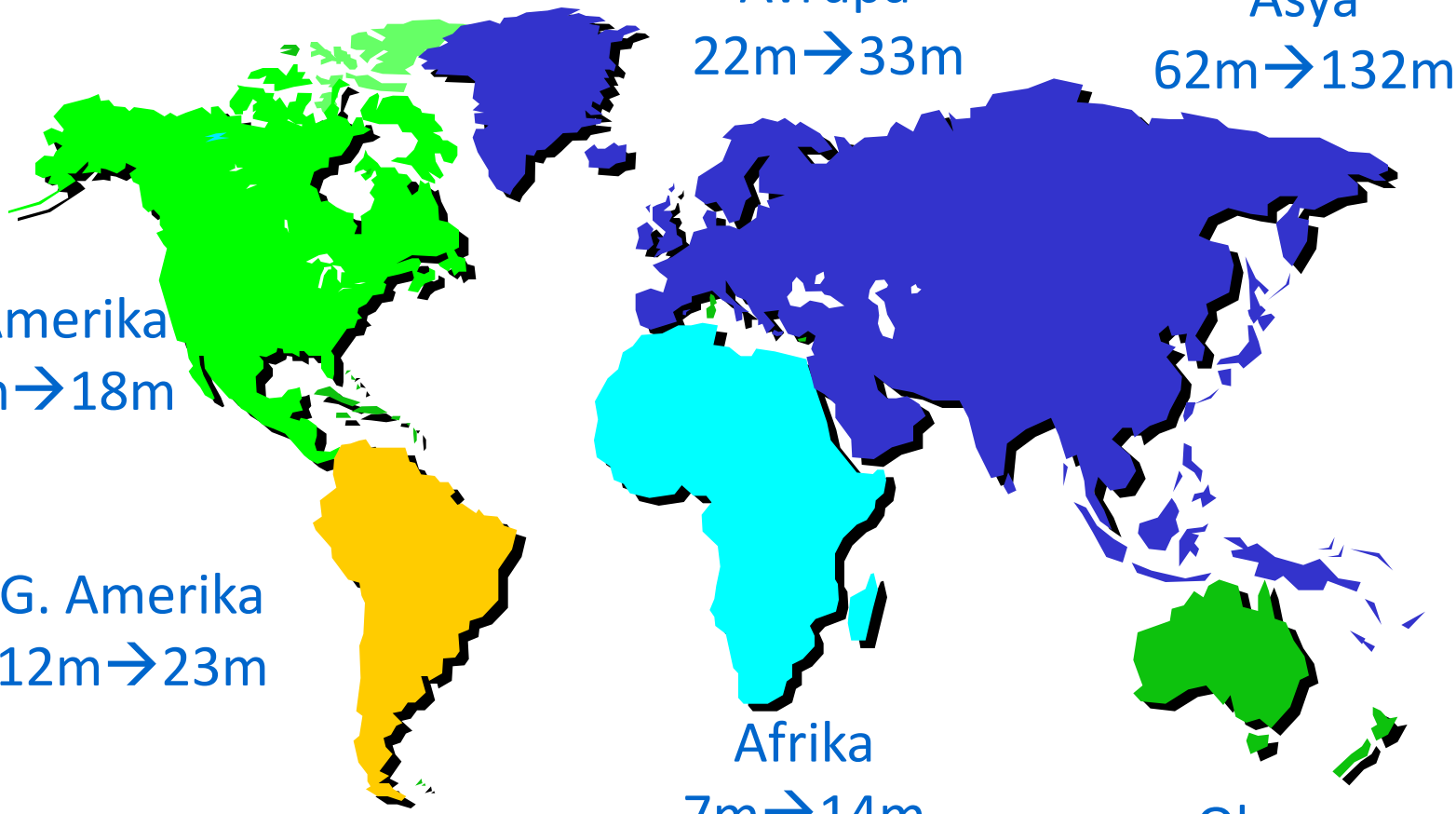

AGACTAACC….
ACGAATCCT….
GGACTTACC….
GCACAACCT….
GGGATTAAC.…

# Genome-Wide Associations GWAS

NHGRI GWA Catalog
www.genome.gov/GWAStudies



# Diyabet oranlarında değişim




1995→2010 110m → 220m

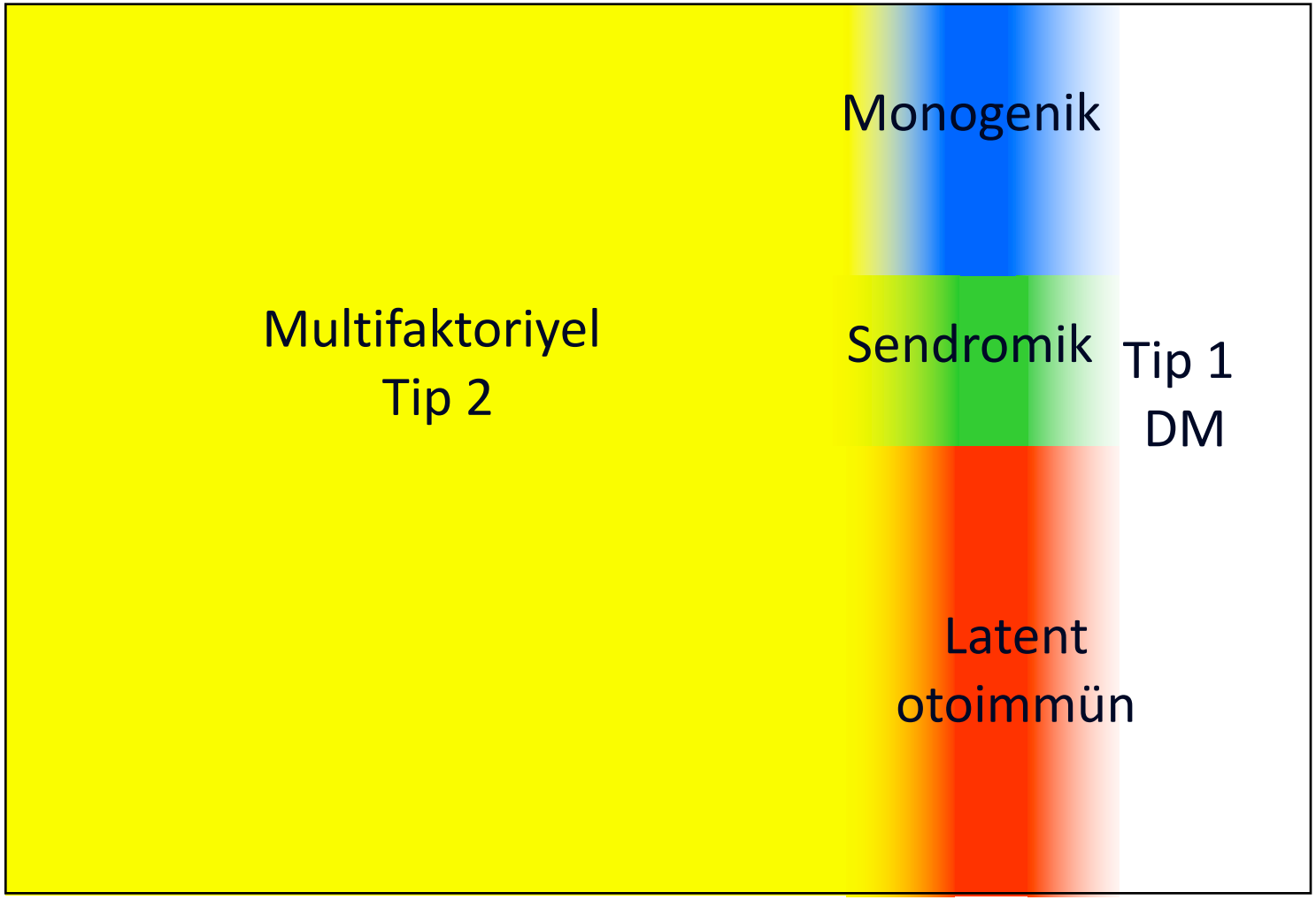
# Tip 2 Diyabet Genetik bir Hastalık

- Ailesel yığılım
- MZ ikizlerde DZ lere göre yüksek konkordans
  - MZ ikizilerde konkordans ~60%
- Göç çalışmaları ile riskin değişmemesi
- Karışık toplumlarda parental köken oranı etkisi
- Genetik temeli destekleyen hayvan modellemeleri
- Sorumlu genler

# Tip 2 Diyabet Çevresel bir Hastalık

- MZ ikizilerde konkordans >60% (yaşam boyu riskleri >%90)
- DZ ikiziler ve kardeşlerde konkordans %25-50
- Prevalansda hızlı değişim genlerle açıklanamıyor
- Çevresel risk faktörleri ve yaşam tarzı ile risk değişiyor
- Erken gelişim ile Tip2 Diyabet riski arasında ilişki erken dönem çevresel etkenler ve genlerle ilişkili

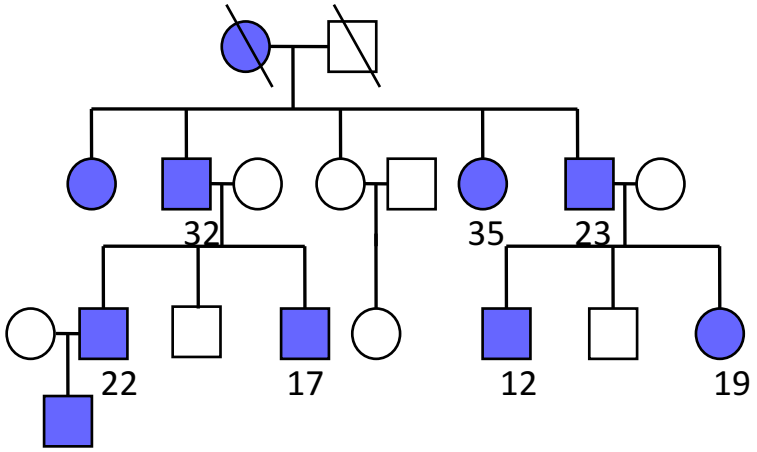
# Diyabet dağılımı



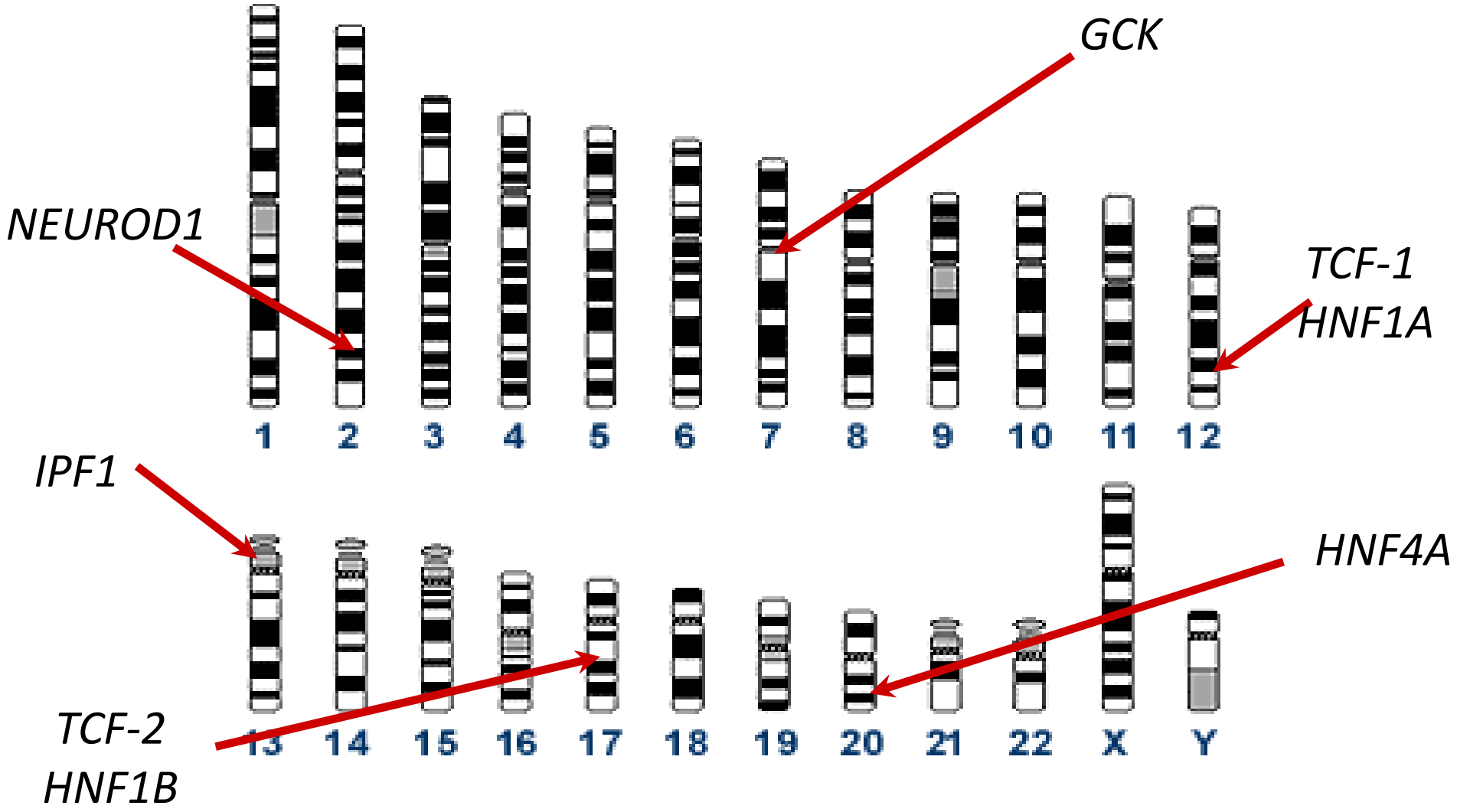
# MODY (Maturity Onset Diabetes of the Young)

- Non-insulin diabet
- 25 yaş öncesi tutulum
- A.  Dominant – En az 3 kuşak

- Klinik, genetik heterojenite (fizyoloji, hastalık seyri)



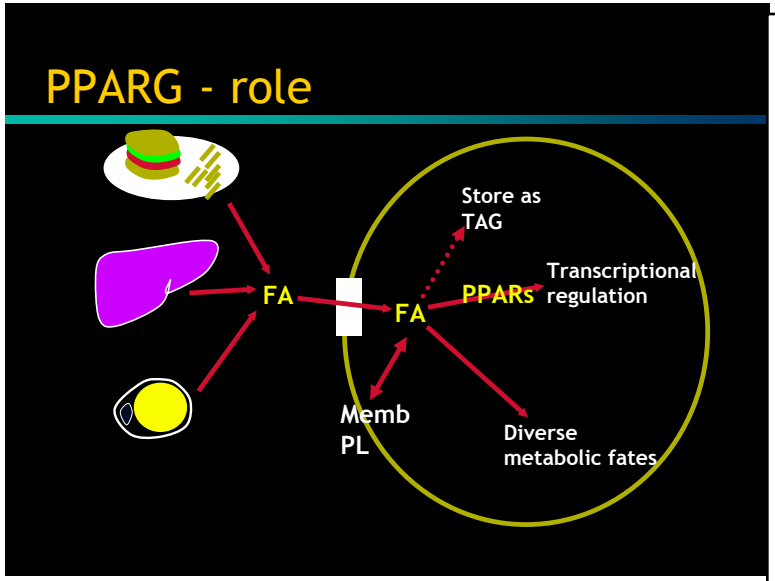
# MODY gen lokusları



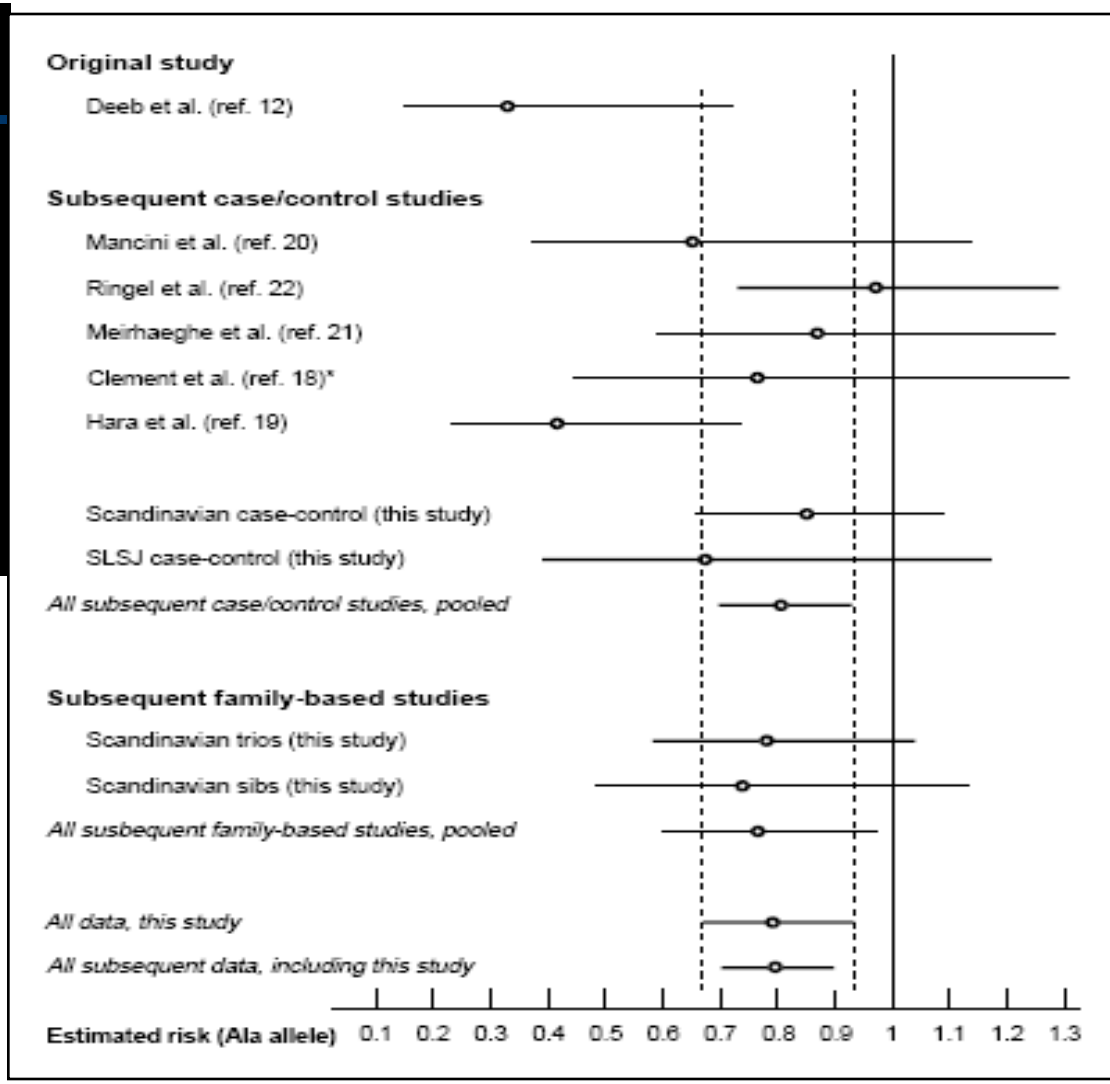
# *PPARG* Pro12Ala ve Tip 2 DM

Peroxisome proliferator-activated receptor gamma

(*çoğu insülin duyarlılığını artıran ilaçların hedefi*)




| | |
|---|---|
| 1.25 | görece risk (RR) |
| 85% | yatkınlık aleli sıklığı |
| ~25% | toplam risk oranı |

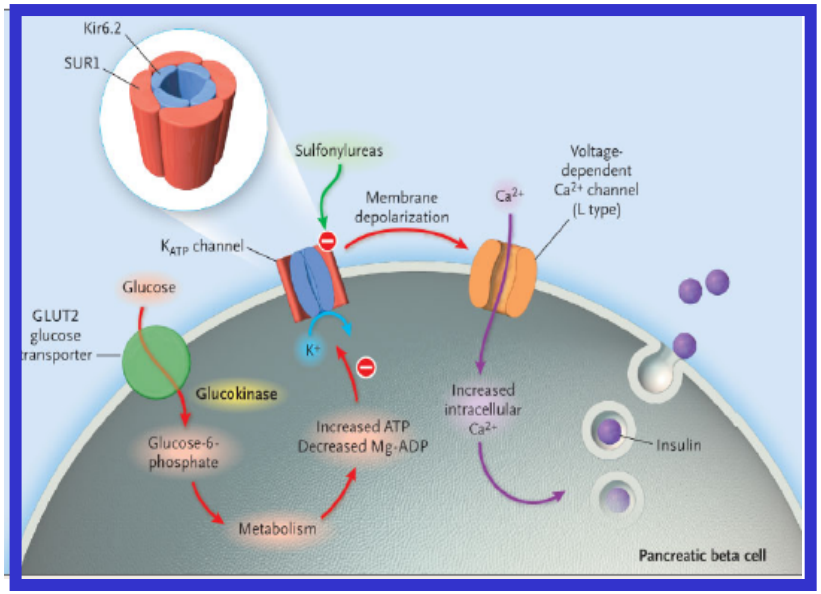


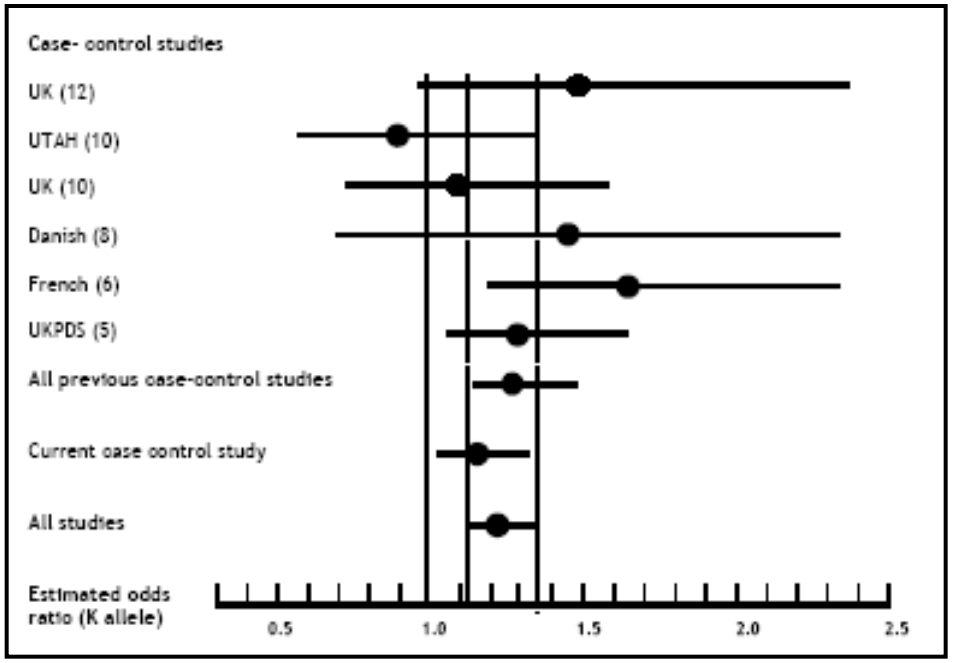

**Altshuler et al, NG, 2000**

# Kir6.2 (*KCNJ11*)

## ATP'ye duyarlı $K^+$ kanal proteini

**Varyasyon: E23K**



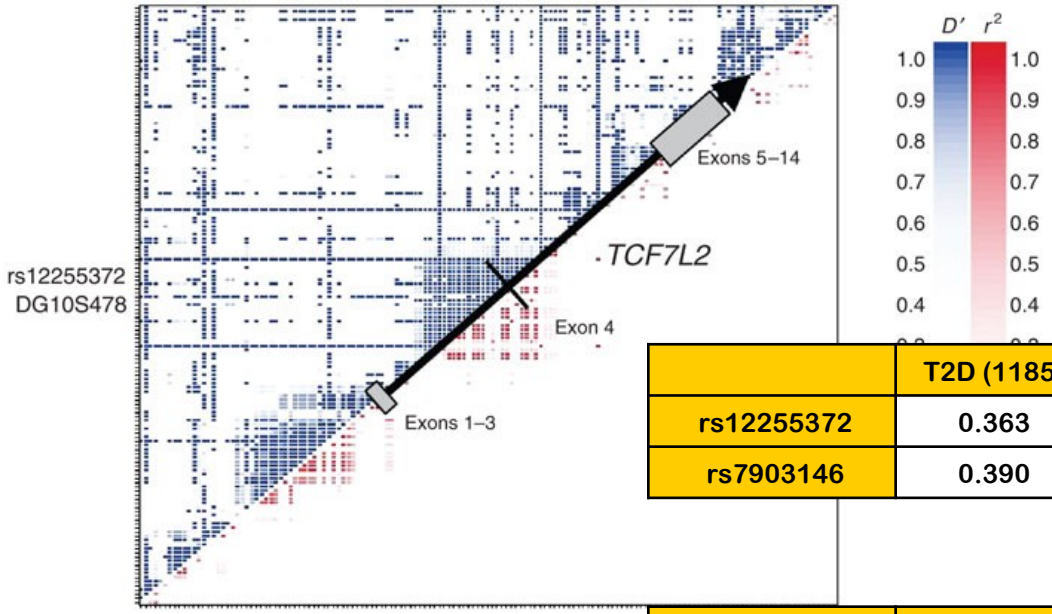




Gloyn et al, Diabetes 2003

| | |
|---|---|
| 1.16 | görece risk |
| 40% | yatkınlık aleli sıklığı |
| ~10% | toplamda risk oranı |

familial persistent hyperinsulinemic hypoglycemia of infancy **(PHHI)** **Tip II Diyabet**

# TCF7L2 *(Transcription factor 7-like 2)*







Grant, Nat Genetics, March 2006

**Izlanda**

| | T2D (1185) | Control (931) | RR (multiplicative) | p (2 sided) |
|---|---|---|---|---|
| rs12255372 | 0.363 | 0.283 | 1.50 [1.31,1.71] | $4.8 \times 10^{-9}$ |
| rs7903146 | 0.390 | 0.299 | 1.45 [1.27,1.66] | $1.6 \times 10^{-9}$ |

**Danimarka**

| | T2D (228) | Control (539) | RR (multiplicative) | p (2 sided) |
|---|---|---|---|---|
| rs12255372 | 0.333 | 0.261 | 1.41 [1.12,1.78] | 0.0041 |
| rs7903146 | 0.355 | 0.274 | 1.46 [1.15,1.85] | 0.0018 |

**ABD**

| | T2D (361) | Control (530) | RR (multiplicative) | p (2 sided) |
|---|---|---|---|---|
| rs12255372 | 0.389 | 0.260 | 1.81 [1.48,2.22] | $9.4 \times 10^{-9}$ |
| rs7903146 | 0.397 | 0.278 | 1.71 [1.40,2.09] | $1.6 \times 10^{-7}$ |

# Diyabet ve duyarlılık